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# The Potential Role of Minoxidil in the Hair Transplantation Setting

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**BACKGROUND.** Over the last decade surgical management of hair loss has become an increasingly popular and satisfying procedure for both men and women, as innovations in donor harvesting, graft size, and hairline design have resulted in consistently natural-appearing hair restoration.

**OBJECTIVE.** In addition, a better understanding of the regulation of the hair-growth cycle has led to advances in the pharmacologic treatment of androgenetic alopecia.

**METHODS.** Currently there are two U.S. Food and Drug Administration (FDA)-approved agents that promote hair regrowth: over-the-counter topical minoxidil solution for men and women and prescription oral finasteride tablets for men. In October 2001, a group of 11 international experts on hair loss and hair transplantation convened to review the physiology and effects of

pharmacologic treatments of hair loss and to discuss the value of administering topical minoxidil therapy as an adjunct to hair transplantation.

**RESULTS.** This article presents the key findings and consensus points among the participants, including their current use of pharmacologic treatments, strategies for optimal results both pre- and postsurgery, and the importance of realistic patient expectations and compliance.

**CONCLUSIONS.** Based on the surgeons' clinical experience, the use of approved hair regrowth agents in hair transplant patients with viable but suboptimally functioning follicles in the region to be transplanted can increase hair density, speed regrowth in transplanted follicles, and complement the surgical result by slowing down or stopping further hair loss.

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HAIR GROWTH is a dynamic process characterized by repeated cycles of active growth (anagen, 2–6 years), involution (catagen, 2–3 weeks), and rest (telogen, 2–3 months).<sup>1</sup> At any one time, approximately 90% of all scalp follicles are undergoing active growth in the anagen phase.<sup>2,3</sup> Temporary or permanent hair loss can be caused by a number of factors, including medication, hair styling, chemotherapy, exposure to chemicals, hormonal and nutritional factors, generalized or local skin disease, chronic disease, and stress. However, the most common type of hair loss, by far, is androgenetic alopecia (AGA; also known as male or female pattern hair loss), which is estimated to affect half of all men and women by the age of 50 years.<sup>3</sup> Androgenetic alopecia is the hereditary thinning of the hair that is induced by androgens in genetically (polygenic autosomal trait) predisposed hair follicles. As a result of these hormones,

particularly dihydrotestosterone (DHT), hair follicles shrink in size and the anagen phase of hair growth becomes progressively shorter, resulting in finer, shorter hairs that provide less scalp coverage. Cycle after cycle, the follicle produces an increasingly fine, wispy hair with less pigment until eventually there is no visible or perceptible growth at all. Studies have demonstrated that AGA is clearly a stressful condition with psychologically detrimental effects on both sexes, particularly for female patients and for individuals who seek professional treatment.<sup>4–6</sup>

## Hair Transplantation

Surgical hair transplantation is an extremely popular treatment method for male and female pattern hair loss. The quality of hair transplantation procedures has improved dramatically over the past decade, and modern techniques and instrumentation have eliminated the cosmetically unnatural “corn row” appearance of hair transplants performed during the 1960s and into the

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**Figure 1.** Straight "pluggy" hairline from 10–25 hair grafts.

1990s (Figure 1).<sup>7</sup> Hair transplantation involves surgical removal of a strip of hair-bearing scalp tissue (usually 8–20 cm long  $\times$  0.6–1.0 cm wide) from the "donor-dominant" hair-bearing areas on the back and sides of the head where the hair follicles are not susceptible to DHT and continue to cycle normally for life. Traditionally the donor hair is divided into grafts containing 10–25 hairs each. Hair on the scalp grows naturally in follicular groupings of one to three hairs and, rarely, as many as five hairs. Thus early harvest and planting techniques using 4 mm punch graphs of 10–25 hairs appear "pluggy" and unnatural. Recent advances in dividing the donor hair strip into natural one- to three-hair follicular units (micrografts/follicular groupings) and strategically and meticulously implanting them into hundreds or thousands of recipient sites in the balding area have created consistently natural-appearing transplanted hair for men and women (Figures 2 and 3).<sup>7</sup>

Key factors that contribute to a successful hair transplant procedure include the density of donor hair, extent of hair loss, and color and caliber of hair, as well as realistic expectations of the patient and physician. Androgenetic alopecia is not affected by hair transplantation and, when untreated, it will continue its steady progression following surgery. A challenge for the hair transplant surgeon is to create a permanent natural hairline and distribution of transplanted hair that anticipates the pattern of future hair loss and that will, over time, remain cosmetically acceptable for the patient and physician. Patients who do supplement surgery with medication can expect to maintain existing hair with medication and add density with surgery. Without medication the density from a transplant will equal the number of hair follicles added in surgery minus the loss of exist-



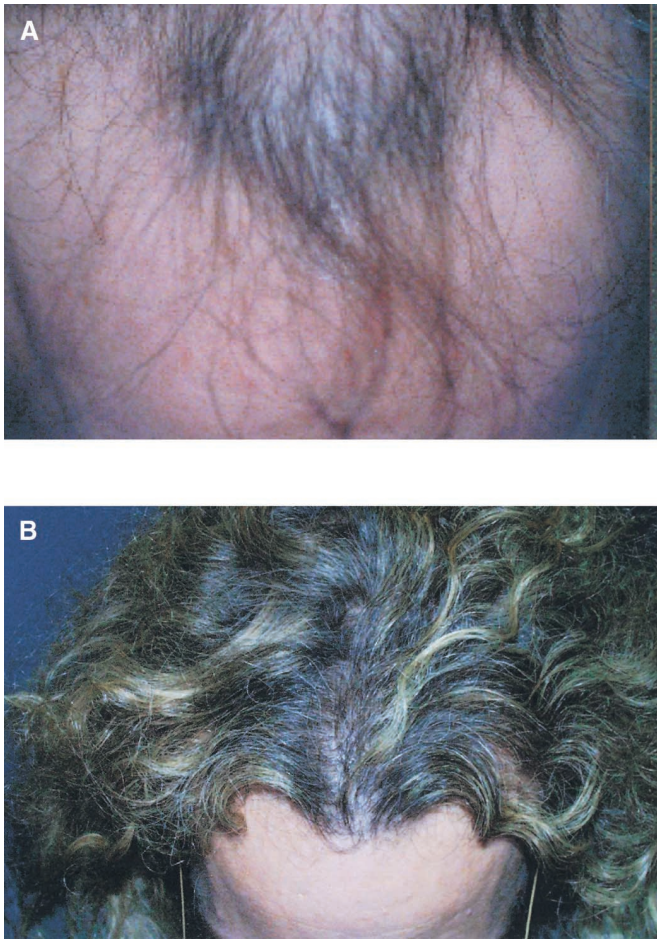
**Figure 2.** (A) Female pattern alopecia Ludwig II-III before hair transplant. (B) After one session 800 1–3 hair grafts.

ing hair. With either route, the transplanted hair must appear natural with or without any medical therapy to maintain existing hair.

### Medical Therapy

A better understanding of the biochemistry and physiology of hair growth and hair loss also has resulted in advances in the medical treatment of hair loss. Currently there are two pharmacologic treatments approved by the U.S. Food and Drug Administration (FDA) to treat pattern hair loss in men: over-the-counter topical minoxidil solution and prescription-only oral finasteride tablets. Well-controlled clinical trials have demonstrated that these agents are safe and effective treatments, inducing





**Figure 3.** (A) Norwood class III-IV male pattern hair loss before transplant. (B) After 2200 1-3 hair grafts frontal scalp.

hair regrowth in many individuals with mild to moderate hair loss.<sup>8-10</sup> For woman, over-the-counter topical minoxidil 2% solution is the only FDA-approved pharmacologic agent for pattern hair loss.

### Minoxidil

In 1979 oral minoxidil was approved for the treatment of patients with severe hypertension.<sup>3</sup> Reports of increased body hair growth in many of the patients using this antihypertensive preparation led to clinical development of a topical formulation of the drug. Minoxidil 2% topical solution via prescription was approved by the FDA for the treatment of androgenetic alopecia in men (1988) and women (1992). In 1996, minoxidil 2% solution was approved for over-the-counter use in men and women with androgenetic alopecia. Subsequently, in 1997, minoxidil 5% topical solution was approved for nonprescription use in men with androgenetic alopecia.<sup>3</sup>

Although its exact mechanism of action remains unknown, topical minoxidil may act as a nonspecific biologic response modifier. The vasorelaxant effect of minoxidil sulfate, the active metabolite of minoxidil, results primarily from opening potassium channels.<sup>11,12</sup> However, the mechanism of action of topical minoxidil with respect to the stimulation of hair growth appears to be independent of vasodilation.<sup>3</sup> Minoxidil topical solution acts directly to enlarge miniaturized follicles and the diameters of the hair shafts they produce. Telogen hair follicles are converted to anagen hair follicles, and the anagen phase of hair growth is prolonged, thus slowing the progression of hair loss.<sup>3</sup> Although the growth phase may be prolonged, the follicle will continue to cycle, thus several months' use (up to 1 year) may be necessary before optimum potential hair growth is achieved. An important factor that favors regrowth is the presence of a large number of partially miniaturized follicles that are still producing hair 3/8 inch or more in length.

Studies of minoxidil topical solution in men and women have demonstrated significant increases in both hair count<sup>13</sup> and hair weight<sup>8,14</sup> compared with a vehicle placebo control, with the minoxidil 5% solution significantly more effective than the 2% solution in male subjects.<sup>13</sup> Recently Rundegren and Trancik<sup>15</sup> evaluated the effects of minoxidil 5% and 2% topical solution on stabilization of hair loss in men and women with androgenetic alopecia. Stabilization was defined as a combination of unchanged hair status and hair regrowth. This retrospective analysis was based on comparative data obtained from four randomized, double-blind, placebo-controlled trials ( $n = 1054$ ) and from a major postmarketing surveillance study. The stabilization response (ie, the percentage of patients who had unchanged hair growth or regrowth) varied from 87 to 88% in female studies of minoxidil 2% ( $n = 438$ ) and 75 to 96% in male studies of minoxidil 5% ( $n = 616$ ) (Table 1). Both concentrations of minoxidil topical solution were significantly superior to placebo. The response rates noted in placebo patients is likely due to the excipient propylene glycol. Data from the postmarketing surveillance study found that 80% ( $n = 11,000$ ) of patients being treated with minoxidil 2% topical solution reported a diminished rate or stopping of hair loss.<sup>15</sup> Studies focusing on other indications of hair loss, although not approved in the product labeling, have shown that minoxidil stimulates hair regrowth in patients with patchy and extensive alopecia areata and reduces the duration of alopecia caused by chemotherapy.<sup>16,17</sup>

Several studies have examined the use of minoxidil as an adjunct to hair transplantation surgery in men with androgenetic alopecia.<sup>18-20</sup> In an uncontrolled study of 12 male patients with androgenetic alopecia, minoxidil 3% topical solution was administered twice a day to the transplant area starting 48-72 hours after hair

**Table 1.** Stabilization of Hair Loss With Minoxidil Topical Solution

Study	Gender	Duration (weeks)	Patients with stabilization <sup>a</sup> of hair loss, % (n)		
			5%	2%	Placebo <sup>b</sup>
1	Male (n = 295)	32	96% (163)	90% (79)	67% (53)
2	Male <sup>c</sup> (n = 321)	48	75% (134)	77% (142)	56% (40)
3	Female (n = 193)	32	85% (74)	87% (84)	73% (35)
4	Female (n = 245)	48	89% (102)	88% (108)	69% (35)

<sup>a</sup>Stabilization of hair loss is either an increase or unchanged number of nonvellus (pigmented) hairs at the end of the study compared with baseline hair counts.

<sup>b</sup>The response rate noted in the placebo group is likely due to the excipient propylene glycol.

<sup>c</sup>Reference 13.

Adapted from Rundegren and Trancik.<sup>15</sup>

transplant surgery.<sup>18</sup> Two patients demonstrated hair growth without the usual shedding 2–4 weeks after surgery and two additional patients had regrowth within 4 weeks after postsurgical telogen effluvium. This is far sooner than the typical 3–5 months.

In another uncontrolled trial of 16 male hair transplant patients with androgenetic alopecia,<sup>19</sup> minoxidil 2% was administered for 4 weeks prior to surgery, interrupted for 3 weeks, then restarted and continued for 3 months after surgery. The study found that in 71% of grafts, partial or total hair was still growing without the usual shedding that occurs 2–4 weeks after surgery.

The effectiveness of administering minoxidil prior to hair transplant surgery was also reported by Roenigk and Berman.<sup>20</sup> In this double-blind trial, 12 males with androgenetic alopecia were randomized to have either minoxidil 2% topical solution or placebo applied to the donor area for 6 weeks prior to transplantation and to recipient areas for 17 weeks after surgery. After 17 weeks, significantly less grafted hair was lost by minoxidil-treated patients compared with placebo-treated patients (22% versus 52%;  $P = .001$ ).

## Finasteride

Finasteride was originally developed for the treatment of benign prostatic hypertrophy. It differs from minoxidil in that finasteride is a competitive inhibitor of the intracellular enzyme type 2  $5\alpha$ -reductase and inhibits the conversion of testosterone to the more potent metabolite, dihydrotestosterone.<sup>9,10</sup> Dihydrotestosterone is thought to act directly on the hair follicle and is a contributing factor in androgenetic alopecia. Oral administration of finasteride produces a reduction in circulating and skin levels of dihydrotestosterone without reducing testosterone. Finasteride 1 mg/day significantly lowers levels of dihydrotestosterone in the scalp, retards progression of hair loss, and induces hair growth in men with androgenetic alopecia. Finasteride is not indicated for use in women. Because  $5\alpha$ -reductase inhibitors may cause abnormalities of the

external genitalia in the male fetus, women who are or may become pregnant should not use finasteride nor should they handle crushed or broken tablets.

Data from three randomized, double-blind, placebo-controlled trials demonstrated that finasteride significantly increased hair counts and improved scalp coverage of both the vertex and frontal regions compared with placebo.<sup>21–23</sup> The greatest benefit with regard to hair counts occurred within the first year of therapy with finasteride. Scalp coverage, however, may progressively increase with a longer duration of use. There are no published studies of the use of finasteride as an adjunct to hair replacement surgery in men with androgenetic alopecia, although studies of the effects of finasteride when used with hair transplantation are currently under way.

## Other Therapies

There are a number of prescription products that are approved for use in other medical conditions that may have some theoretical effect on hair loss. These include spironolactone, flutamide, progesterone, cyproterone acetate, and cimetidine. However, well-controlled trials in patients with androgenetic alopecia are lacking.<sup>24</sup> In addition, there are countless unapproved treatments—many with herbal or “natural product” bases—that are sold directly to patients. Neither the efficacy nor the safety of the majority of these products for treatment of pattern hair loss have been established; many of the ingredients or products have not been approved by the FDA.

## Current Use of Nonsurgical Medical Treatments in the Hair Transplant Setting

Recently a group of 11 international experts on hair loss and hair transplantation convened to review the physiology and effects of nonsurgical medical treatments of hair loss and to discuss the value of using topical minoxidil therapy as an adjunct to hair transplantation. The round-table consensus meeting was held during the 9th Annual

**Table 2. Minoxidil as an Adjunct to Hair Transplantation: Key Consensus Points**


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Educating patients about medical treatments is essential to managing expectations and improving compliance.
Minoxidil treatment should be started as soon as possible prior to surgery to
Stabilize hair loss.
Increase the number of hairs in anagen phase.
Increase hair weight and density by enlarging miniaturized, suboptimal follicles.
Decrease postsurgical telogen shedding.
Following surgery, minoxidil treatment can
Prolong the anagen phase.
Promote hair growth in transplanted grafts.
Reduce postsurgical shock and telogen effluvium.
Adjunctive minoxidil treatment has particular advantages for the following hair transplant patients:
Female patients, whose thinning is typically diffuse.
Younger male patients with diffuse thinning and a family history of extensive loss.
Patients desiring reconstruction of the posterior scalp.

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Meeting of the International Society of Hair Restoration Surgery in Puerto Vallarta, Mexico, October 2001. The following presents the participants' key observations and points of consensus from their discussion (Table 2).

The roundtable participants noted that the majority of prospective hair transplant patients report previous use of nonsurgical medical treatments prior to seeking an initial consultation about hair transplant surgery. Approximately 40% of the panel members' prospective hair transplant patients have used minoxidil (range 15–90%) and about 15% have used finasteride (range 10–50%). Fewer patients (about 5–10%) have tried a combination of both agents. However, at the time of initial consultation, many of these patients were not using minoxidil and/or finasteride on a regular basis, which is essential to achieving optimal results with these products. In addition, more than half of their new patients had experimented with other, unapproved preparations. Several roundtable participants reported that patients' negative experiences with some of the costly, unproven preparations advertised in magazines and over the Internet have resulted in a great amount of cynicism about the treatment of hair loss in general. Moreover, a few roundtable participants noted that some of their prospective patients are unaware of the available approved medical treatments for hair loss.

Additional patient education about medical treatments is critical in managing patients' expectations and improving patient compliance. Depending on their age, degree of hair loss, and comfort level with their current appearance, approximately 15–20% of the surgeons' prospective hair transplant patients are started on nonsurgical medical treatments rather than proceeding with a hair transplant.

All members of the consensus panel currently recommend minoxidil and/or finasteride, when indicated, to a large percentage of their patients, whether as an initial treatment for their hair loss or as an adjunct to hair transplantation surgery. More than half of the surgeons recommend minoxidil and finasteride equally. As the agents have differing mechanisms of action that the surgeons believe may convey a synergistic effect, more than 70% will sometimes recommend a combination of minoxidil and finasteride to their male patients. Recommendations center primarily on efficacy, patient preference, and cost. Panel members noted that both agents are safe and well tolerated, although there is a general perception among their patients that minoxidil is a safer treatment. Panel members noted patient concern about finasteride's possible effect on sexual function. However, in clinical studies, approximately 2% of men reported one or more sexual side effects during finasteride treatment (including decreased libido, erectile dysfunction, and ejaculation disorder) compared with 1% placebo.<sup>23</sup> These effects may diminish over time, even with continued use of the drug, and resolve off therapy.

Because minoxidil and finasteride are routinely used as adjuncts to hair transplant surgery, it is important to obtain a detailed history of the patient's past use of these agents. This may help in the selection of an agent that is both efficacious and addresses patient preferences. It may also provide a gauge as to the level of patient education and follow-up with regard to potential compliance issues that is needed.

### Strategies for Optimal Results With Adjunctive Minoxidil Treatment

For patients with existing thinning hair undergoing hair transplantation, all of the hair transplant surgeons strongly recommend the use of one or both of the FDA-approved medications to limit further loss and optimize the density from a hair transplant (Figure 3). Recognizing that it usually takes about 2–4 months to see demonstrable effects with minoxidil treatment, the group generally recommends that their patients begin treatment as soon as possible following the initial transplant consult visit. Based on their clinical experience with their patients, the majority of panel members noted the following advantages of regular medical treatment with minoxidil prior to surgery: stabilization of progressive hair loss, increased number of hairs in the anagen phase, increased hair weight and density, and decreased postsurgical telogen shedding. Overall the group agreed that the primary benefit of minoxidil application was within and surrounding the area of hair loss, although a few panel members speculated that its use in the donor area may convert some telogen follicles into anagen follicles, making them more visible during the graft preparation pro-

cess and possibly even increasing the number of units available for implantation.

Reported potential benefits of regular minoxidil administration following hair transplant surgery included an increase in the number of anagen hairs, promotion of hair growth in the transplanted grafts and surrounding areas, and reduction of postsurgical shock and telogen effluvium. In addition, as minoxidil promotes hair regrowth and increases the diameter of the hair shaft, its use can add additional density and complement the surgical result. Panel members highlighted particular advantages of minoxidil use among the following groups of hair transplant patients: female patients, whose hair thinning is typically diffuse and for whom minoxidil 2% is the only currently approved option; younger male patients with diffuse thinning and a family history for extensive loss, whose androgenetic alopecia will continue to progress without treatment following the hair transplant; and patients desiring reconstruction of the posterior scalp (the "whirl" area).

Most of the surgeons advise their patients to stop using minoxidil at least 2–3 days prior to surgery (range 1–14 days) to minimize skin irritation and to reduce a theoretical risk of increased intraoperative bleeding secondary to vasodilation. Similarly the surgeons prefer to reinstitute minoxidil administration between 2 and 14 days after surgery. This allows the epithelium time to heal and minimizes the potential for theoretical damage to the transplanted grafts from the propylene glycol-based vehicle in which minoxidil is administered. In contrast, finasteride use is uninterrupted in the pre- and postsurgical period.

The majority of the surgeons reported observations of greater hair density and increased scalp coverage in their male and female patients with minoxidil 5% compared to minoxidil 2%, as well as earlier recognition of results. Most panel members noted no increase in adverse effects among their patients with the 5% solution. A few surgeons mentioned reports of increased precipitation on the scalp (powdery residue) from a small minority of their patients, and suggested that the additional benefit of the 5% solution may be weighed, to an even lesser extent, against a potential for increased scalp irritation and facial hypertrichosis in women. The hypertrichotic effect on the scalp and other sites is reversible and can disappear despite continued use of the product.<sup>3</sup>

As discussed, most panel members recognized the potential advantages of the use of minoxidil in combination with finasteride, based primarily on the different mechanisms of actions of these agents. However, controlled clinical data demonstrating additive or synergistic efficacy and safety in humans with this combination are lacking.

The importance of postsurgical follow-up visits and on-going patient counseling was acknowledged by all

of the participants, especially for their patients who continue to use medical therapy to complement the results of hair transplantation. To enhance surgical outcomes, slow progression of future hair loss, and to prevent the rapid shedding that may accompany discontinuation of pharmacologic treatments, the panel members generally recommended their continued, indefinite use. While the scheduling of follow-up visits varied among the participants, most reported seeing their patients approximately 1–2 weeks after surgery, and every 3 months after that for the first year, followed by visits every 6–8 months thereafter.

More than a decade of successful use of topical minoxidil in the treatment of patients with pattern hair loss in the nonsurgical setting, coupled with encouraging results from the three small preliminary studies<sup>10–12</sup> of minoxidil topical solution as an adjunct to hair transplant surgery, has facilitated its acceptance and successful use in this setting among specialists. However, the group was unanimous in advocating for additional, larger clinical studies, which would serve to both strengthen their recommendations and to aid in patient education and compliance.

## Conclusion

Minoxidil and finasteride are proven, safe, and effective medications for androgenetic alopecia. The use of topical minoxidil and/or oral finasteride in hair transplant patients with viable but suboptimally functioning follicles in the region to be transplanted can add to the density and complement the surgical result by slowing down or stopping further hair loss. Results from preliminary uncontrolled clinical trials suggest that minoxidil may speed regrowth in transplanted follicles, prolong the anagen phase, and slow progression of future hair loss. Controlled clinical trials are needed to substantiate these preliminary data in this patient population and determine what impact other factors such as patient education and compliance may have in enhancing hair transplant outcomes.

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## Commentary

Though it is assumed by those physicians performing hair transplantation that the adjunctive use of either finasteride or minoxidil is beneficial to those patients having this procedure, there is little information available substantiating its value. This review with comments by 11 respected hair transplant surgeons is very valuable in confirming this opinion. The fact that 100% strongly recommend one or both drugs to their hair transplant patients and 70% sometimes recommend both is reassuring. The published studies with minoxidil report better results than I have seen personally, so it is particularly interesting to see that this panel confirms the experience of the published authors. The potential benefits of these drugs in conjunction with hair transplantation are enormous. Hair transplantation is the only method available to re-

place lost hair in a predictable manner. However, the ability to preserve hair that is subject to androgenetic alopecia allows for better blending of the transplant with the residual hair, better density, and decreased total numbers of transplanted hairs—all resulting in a more natural appearance. The review of the literature helps understand all of these potential benefits and the panel's comments confirm that these expectations may be real. Further studies to objectively confirm these opinions, is the next step.

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